

**RESPIRATORY STUDIES
IN ASTHMATIC CHILDREN DURING
SYMPTOM-FREE PERIODS**

SIGNIFICANCE FOR CLINICAL ASSESSMENT

BY

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Diss. med.
Stockholm. Karolinska Institutet

6 MAJ 1959

STOCKHOLM 1959

FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET
AT KAROLINSKA SJUKHUSET, STOCKHOLM

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Almqvist & Wiksells

BOKTRYCKERI AKTIEBOLAG

UPPSALA 1959

This survey is based on the following papers:

- I. ENGSTRÖM, I., KARLBERG, P. and KRÆPELIEN, S.: Respiratory Studies in Children. I. Lung Volumes in Healthy Children, 6–14 Years of Age. *Acta pædiat.*, 46: 277, 1956.
- II. KRÆPELIEN, S., ENGSTRÖM, I. and KARLBERG, P.: Respiratory Studies in Children. II. Lung Volumes in Symptom-free Asthmatic Children, 6–14 Years of Age. *Acta pædiat.*, 47: 399, 1958.
- III. KRÆPELIEN, S.: Respiratory Studies in Children. III. Lung Volumes in Children with Prurigo Besnier (Atopic Dermatitis). *Acta pædiat.*, 47: 412, 1958.
- IV. KRÆPELIEN, S.: Respiratory Studies in Children. IV. The Effect of Bronchodilator Drugs on the Lung Volumes in Symptom-free Asthmatic Children. *Acta pædiat.*, 47: 549, 1958.
- V. ENGSTRÖM, I., KARLBERG, P., KRÆPELIEN, S. and WENGLER, G.: Respiratory Studies in Children. V. Maximal Breathing Capacity in Healthy and in Symptom-free Asthmatic Children, 7–14 Years of Age. *Acta pædiat.*, 47: 560, 1958.
- VI. ENGSTRÖM, I., ESCARDÓ, F. E., KARLBERG, P. and KRÆPELIEN, S.: Respiratory Studies in Children. VI. Timed Vital Capacity in Healthy Children and in Symptom-free Asthmatic Children. *Acta pædiat.*, 48: 114, 1959.
- VII. KRÆPELIEN, S.: Respiratory Studies in Children. VII. A Longitudinal Study of the Lung Volumes in Asthmatic Children during Symptom-free Periods. *Acta pædiat.*, 48, 1959 (in press).

References to these papers are indicated by the Roman numerals I–VII as above.

Acknowledgements

My gratitude is due firstly to my former chief, Professor *Arvid Wallgren*. It was at his initiative that the first Outpatient Department for Allergic Children was opened in Sweden, originally at the Pediatric Clinic of Norrtulls Sjukhus, which has been the incitement for further developments in the care of allergic children in our country. For the ten years during which I had the great benefit of attending to the allergic children under his superintendence, I am greatly indebted. Without his interest and stimulation these studies could not have been brought to completion.

I wish to extend my thanks also to Professor *John Lind* for his generous help and encouragement in my continuing work at the Pediatric Clinic of Karolinska Sjukhuset and for the great interest with which he followed the work here. Professor *Torgny Sjöstrand* has followed the progress of these studies throughout in a stimulating manner and his expert advice and direction have been of extreme value. I am most grateful to him.

My warm gratitude goes to my colleagues on the team at the Physiological Laboratory of the Pediatric Clinic. In particular I wish to thank Dr. *Inga Engström* and Docent *Petter Karlberg* who have both given me invaluable assistance from start to finish.

I thank Mr. *Rolf Jansson* for his work on the statistical analysis and Mr. *John Hogg* for his translation.

Finally, I express my gratitude to the nurses, Mrs. *Britta Jansson*, Miss *Kerstin Werner*, Miss *Ulla Heyman*, Mrs. *Siv Åsander* and Mrs. *Inger Linde*, each of whom has helped me in the capacity of technical assistant at different periods of this study.

The carrying out of these studies has been made possible by generous grants from The Swedish Association against Tuberculosis and Other Social Diseases.

Stockholm, March 1959.

Sven Kræpelien



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Respiratory Studies in Asthmatic Children during Symptom-free Periods

Significance for Clinical Assessment

by SVEN KRÆPELIEN

Allergic diseases in children are a very common occurrence, and the general *Introduction* practitioner as well as the pediatrician is in constant touch with children who manifest allergic symptoms. Of the allergic diseases the main interest is centered on bronchial asthma, both because of its prevalence and its chronicity, even in childhood, and the invalidity it brings in its course.

Bronchial asthma is characterized by a wheezing dyspnoea due to obstruction of breathing caused by swelling of the mucous membrane and spasm of the smaller bronchi and bronchioles and increased secretion in their lumina. The typical feature is its intermittent course with periods of acute attacks between clinically more or less symptom-free intervals. In the initial stage of the disease the bronchial obstruction and its consequences are probably temporary. Repeated attacks or lengthy periods of obstructed expiration may lead to permanent changes in the lungs.

The care of asthmatic children is a delicate matter and requires much time. The primary factor, the actual allergy, and a number of secondary factors affecting the allergic process, such as infection, psyche, and climate, have all to be considered. In the first place the direct causative agents must be traced and eliminated from the child's environment, or reduced in their effect through specific or non-specific hyposensitization. Then the role of the secondary factors must be evaluated and their effect eliminated or reduced.

As a consequence of the prevalence of allergic diseases, and also of the difficulties of diagnosis and therapy, special departments for allergic children have been started in recent decades at the large pediatric clinics in Europe and the United States. In Sweden, the first department of this kind was opened in 1947 at the Pediatric Clinic of Karolinska Institutet, now associated with Karolinska Sjukhuset.

*Incidence of
bronchial
asthma in
childhood*

Many observations suggest that childhood asthma has increased during the last decades, but there are still no studies which have proved this statistically. In Sweden, based on school medical reports covering 247,000 children throughout the country, the author (1954) found an asthma incidence of 0.7 per cent (7). From a less numerous material, but collected in a roughly similar manner, Eriksson-Lihr (1955) reported the incidence among school children in Helsinki to be 0.7 per cent (4), while Frandsen (1958) gave the figure of 0.8 per cent asthmatics among school children in Copenhagen (6). A direct questionnaire addressed by the author to all school doctors and nurses in the Stockholm elementary schools, however, led to a return of 1.4 per cent asthmatics among roughly 60,000 pupils (7), thus double the figure quoted for the whole country. A large group—0.4 per cent of all children—was kept from normal school attendance and intercourse with schoolfellows because of asthma, while the remaining 1.0 per cent had had only brief and temporary periods of illness. The difference found by the author between Stockholm and the rest of the country is probably not a real one, but due rather to the more thorough method of collecting the Stockholm material. There is reason to suppose that the higher figure of 1.4 per cent is more representative for the country as a whole. This would mean that some 10,000 school children in Sweden have asthma. As the disease usually makes its first appearance between the ages of 2 and 3 (sometimes even during infancy), the total number of asthmatic children must be considerably higher. Among the 50 million children in the U.S.A., it is estimated that there are 2.5 million asthmatics, i.e. 5 per cent (9). Thus childhood asthma involves serious social problems in view of its wide prevalence and the demands for efficient care.

*Prognosis for
bronchial
asthma in
childhood*

The prognosis of asthmatic children is illustrated by certain follow-up studies. Flensburg (5) followed up some 300 asthmatic children who had received only symptomatic treatment during observational periods of 5 to 18 years, though at the same time attempts were made to eliminate the allergens. He found that asthma disappeared in only 40 per cent after, on an average, 7.4 years of illness. The same material was reexamined by Ryssing (11) 13 years later, and he found that, of the 120 patients who were free from attacks at the time of Flensburg's examination, 59 had experienced symptoms again and 43 of them still had symptoms. He concludes "that childhood asthma tends but little to spontaneous cure since no more than about 30 per cent become symptom-free after the age of puberty without specific treatment". Rachemann and Edwards (10) made a study of some 450 persons who had received various kinds of therapy during childhood (specific hyposensitization, vaccination, etc.). Twenty years later 71 per cent had become free from asthma during their teens and only 15 per cent still had mild asthmatic symptoms. Unger et al. (12) reported on some 300 specifically hyposensitized asthmatic children, of whom

32 per cent had become free from symptoms and 60 per cent had improved after observation periods of 1 to 30 years. The author, in cooperation with Engström, (3), followed 110 asthmatic children, all of whom had received specific hyposensitization for manifest allergies (established by anamnesis, skin tests and provocation tests) and found 26 per cent free from symptoms and 58 per cent improved after periods of 2 to 4 years. Along with the specific hyposensitization these children received other anti-allergic treatment.

In the various studies reported the principles of treatment have varied and the results are difficult to compare, especially in view of the lack of fixed criteria for "freedom from symptoms" and "improvement", and of the considerable differences between the periods of observation. It is delicate, therefore, to draw conclusions regarding the difference in prognosis for patients who do or do not receive anti-allergic treatment. There is obviously a need of further investigating the effect of different methods of treatment.

It is well known that during acute attacks the pulmonary function of asthmatic children and adults deviates from the normal. Even in intervals between attacks, asthmatic children who are severely affected have poor body development with deformity of the chest, and are easily fatigued, which may be due partly to a prolonged fall-off in physical activity, but it is caused in all probability by a disturbance of the pulmonary function. During the author's continuous work with a large group of asthmatic children, the need became increasingly apparent to include studies of lung function in the examinations. It was considered that such a procedure, in association with clinical data and other laboratory findings, should increase the certainty of the clinical evaluation of the individual case, especially in respect of the severity of the asthma, which has an important bearing on the intensity of the care and therapy. It would also permit an objective record to be kept of the effect of different kinds of therapy. By means of longitudinal studies the development and prognosis of the illness could be better assessed. Series of studies under varying conditions would also increase the knowledge of the nature of the possible pulmonary changes involved.

*Use of lung
function tests*

The data on lung function in the pediatric literature is comparatively scanty and the numbers of cases reported are usually small. The author and his co-workers therefore started by making separate studies of different respiratory components, primarily of static lung volumes (II, IV and VII) and ventilation (V and VI). For assessment of the results, parallel studies were made on healthy children (I, V and VI). The studies have proceeded over the past five years.

In this series of studies asthmatic children have been examined during clinically free periods in order to eliminate temporary changes associated with acute asthmatic attacks, and at the same time the effect of symptomatic treat-

*Studies in
symptom-free
periods*

ment. This will suggest as standardized conditions as possible within the individual and between different individuals. The children felt fully healthy, there was no dyspnoea at rest, auscultation findings were normal, and there was no sign of respiratory infection. A further requirement was that for at least three days before each examination they had had no subjective symptoms nor received symptomatic therapy. Many of the children, however, had had a course of specific therapy during the years preceding the lung function tests, and in many cases this therapy was still proceeding at the time of the examination of lung function. With very few exceptions all children examined showed normal physical development according to the standards of Broman, Dahlberg and Lichtenstein (1).

Clinical classification

For correlation of the findings from the various lung function tests with the severity of the child's asthma from the clinical point of view, it was desirable to find a thoroughly clear and objective basis for assessing the severity of the individual case from the available clinical data. In assessment of the severity of asthma, it is important to take into account all conceivable factors, such as present status (including lung X-ray), duration of illness, frequency, intensity and duration of attacks, and degree of invalidity (judged, for example, from the number of days absent from school due to asthma and the inability to endure ordinary physical exertions). As it was difficult to make an objective synthesis of all these factors, it was decided that the clinical evaluation of the severity of illness should be based solely on the frequency of attacks during the year prior to examination. Working on these lines the material was divided into three groups. Group I consisted of mild asthma cases with less than five short attacks a year; Group II moderately severe asthma with five to ten attacks a year and Group III severe asthma with more than ten attacks a year or prolonged status asthmaticus.

Lung volumes in healthy children (I)

In the examination of lung volumes the functional residual capacity (V_{FRC})¹ was determined with a closed spirometer system, using helium as the test gas. The vital capacity (V_{VC}) and its subdivisions were determined by forced inspiration and expiration in conjunction with the determination of V_{FRC} . The residual volume (V_{R}) was obtained from the difference between V_{FRC} and the expiratory reserve volume (V_{ER}). The total lung capacity (V_{TLC}) was also calculated. For assessment of the results obtained in asthmatic children, a study was first made of the lung volumes of 93 healthy children (I). Since lung volumes are related to lung size, and so to body size, the relationships between the different lung volumes and weight, height and sitting height were determined by regression calculations. Of the three measures of body size, height has shown

¹ The nomenclature is that proposed by a committee headed by J. R. Pappenheimer (8).

the best correlation. The boys showed a tendency toward somewhat higher values of lung volumes in relation to height than the girls, but the difference was not statistically significant and accordingly the sex of patients has been disregarded. Body size has less influence on the ratios of functional residual capacity to total lung capacity ($V_{\text{FRC}}/V_{\text{TLC}}$) and of residual volume to total lung capacity ($V_{\text{R}}/V_{\text{TLC}}$) and these ratios have been found very useful for judging pathological conditions in adults. Therefore they were used in these studies, and their correlation to age was investigated and found to be small.

In the determination of the lung volumes of 98 symptom-free asthmatic children (II), classified according to the frequency of attacks into different severity groups, it was found that the functional residual capacity, the residual volume and the total lung capacity, as also the $V_{\text{FRC}}/V_{\text{TLC}}$ and $V_{\text{R}}/V_{\text{TLC}}$ ratios, were significantly higher than the corresponding values for healthy children. An increased functional residual capacity means that the lungs are hyperinflated during quiet breathing. The residual volume was also increased, indicating that the lung is hyperinflated even after maximal expiration. The two-stage vital capacity, on the other hand, did not deviate significantly from the values of healthy children. Since the vital capacity was normal, the absolute increase in total lung capacity was about the same as the increase in residual volume. The group with the most frequent attacks (Group III) showed the greatest changes. The changes in the other two groups, though of less magnitude, were also statistically significant. (In the statistical analysis, Group I and II were lumped together since there were no differences between them.) In all three groups, however, there were individual cases with lung volumes similar to those found in healthy children.

The lung volumes represent static conditions. The introduction of the time factor into determinations of volume gives a measurement of the ventilation, as in the determination of maximal breathing capacity and timed vital capacity.

For determination of the maximal breathing capacity (MBC) the air expired during 15 seconds of maximum forced breathing was collected in a plastic bag and the volume per minute was calculated. By determining the resting minute volume ($\dot{V}$) before MBC, it was also possible to calculate the breathing reserve ($\text{BR} = \frac{\text{MBC} - \dot{V}}{\text{MBC}} \times 100$). Nineteen asthmatic and 46 healthy children were examined (V). Comparing the symptom-free asthmatic children with healthy children, the values both of MBC and BR were significantly lower statistically in the former, indicating a ventilatory disturbance. The large random error of the method, however, makes it difficult to evaluate an individual's values.

*Lung volumes
in asthmatic
children (II)*

*Maximal
breathing ca-
pacity in asth-
matic children
(V)*

Moreover, since the strain on the patient involves a risk of asthmatic symptoms being provoked by the hyperventilation, the method was found to be unsuited for assessing individual cases.

Timed vital capacity in asthmatic children (VI)

Evaluation of the ventilation in single breaths, as in the determination of timed vital capacity, has been found more suitable for detection of ventilatory disturbance (VI). The quantity of air forcibly expired during the first second after a maximal inspiration ($V_{1 \text{ sec}}$) was recorded and related to the vital capacity (V_{VC}). The use of the $V_{1 \text{ sec}}/V_{VC}$ ratio reduces the influence of body size. In an examination of 38 asthmatic and 17 healthy children the asthmatics generally had ratios lower than those in healthy children. The lowest values were in the group with highest attack frequency (Group III), but there was also a significant difference between Group II and healthy children. Both in Groups I and II, however, there were individual cases with normal values. Timed vital capacity tests have thus proved that most asthmatic children, even during symptom-free periods, have signs of a disturbed ventilation which assumes greater severity the more frequent the asthma attacks.

These different studies of respiration show that, even in symptom-free periods, the lung function of asthmatic children, considered as a group, differs from that in healthy children in the form of hyperinflation of the lungs and diminished capacity of forced expiration. The changes are most marked in children who have the highest attack rate. In view of the selection of the children examined, comprising patients with varying duration and varying intensity of illness, and of the criteria adopted for freedom from symptoms, these findings of disturbed lung function may represent cross-sectional conditions in symptom-free asthmatic children.

Lung volumes in eczema children (III)

Since even mildly affected asthmatic children often differ in respect to lung volumes from healthy children, the question arises whether allergic children in general, in view of their special constitution, differ in their lung physiology from healthy individuals. Examinations of children with allergic skin lesions (Prurigo Besnier) but no asthmatic symptoms showed no difference in lung volumes from healthy children (III). Consequently there are no data to suggest that an allergic constitution alone might be the cause of the changes in lung volumes found in symptom-free asthmatic children.

Effect of bronchodilator drugs on lung volumes in asthmatic children (IV)

The lung function during severe asthmatic attacks with the marked bronchial obstruction indicates the most likely origin of the disturbances found in the symptom-free asthmatic children. Bronchial obstruction leads to a rise in the resting expiratory level. The resulting hyperinflation causes an expansion of the thorax. If the bronchial obstruction persists for a lengthy period, it may lead to emphysema, by which is meant "a pathological

condition of the lung characterized by reduction or loss of elastic fibres, tearing of alveolar septa and decrease in the pulmonary capillary bed" (2). All degrees of affection may occur, from a temporary hyperinflation caused by acute bronchial obstruction to a continuous hyperinflation in form of emphysema, depending on frequency and intensity of the asthmatic attacks, on ability of the lung to return to or approach its normal function in the asymptomatic intervals, and on the duration of the illness.

The nature of the changes found (described above) has been studied by examining the pulmonary function before and after administration of two different bronchodilator drugs (IV). The effect of each of these drugs on lung volumes was tested on 15 asthmatic children who manifested signs of hyperinflation of the lungs during periods when asthmatic symptoms were absent. The two bronchodilator drugs in question were Isoprenaline in aerosol form and Aminophylline (theophylline ethylenediamine) intravenously. The effect on bronchi and bronchial mucous membrane may be regarded as local after administration of Isoprenaline, while that of Aminophylline is more general. To the bronchodilator effect of Aminophylline a cardiovascular action on the pulmonary circulation, may be added; to which extent, however, is difficult to assess. A significant lowering of residual volume was observed after administration of each drug, and of functional residual capacity only after Isoprenaline, but there were still distinct signs of hyperinflation. The reason for the persistent hyperinflation may be either that the drugs only partially removed the bronchial obstruction, or that some parenchymatous changes are present, as in emphysema. The normalizing effect of these drugs on the lung volumes shows that the hyperinflation in these cases is at least partially of a functional character.

The results of the timed vital capacity tests further support the view of functional origin of the hyperinflation. The volume $V_{1 \text{ sec}}$ depends partly on the size of the individual and partly on obstructive and restrictive impediments to breathing. If $V_{1 \text{ sec}}$ is related to V_{VC} ($V_{1 \text{ sec}}/V_{VC}$), the resulting value is not appreciably influenced either by the size of the individual or by restrictive impediments to the breathing, since these two factors affects both V_{VC} and $V_{1 \text{ sec}}$. Thus in cases with normal V_{VC} a lowered ratio $V_{1 \text{ sec}}/V_{VC}$ indicates a bronchial obstruction.

The reversibility of the disturbance of lung function was followed in a longitudinal study (VII). The lung volumes of 18 asthmatic children, who initially exhibited pathological lung volumes during symptom-free intervals, were determined during symptom-free intervals roughly two and four years later. Both before and during the follow-up, the children had received anti-allergic treatment. The hyperinflation successively diminished. The first of the lung volumes to become normalized was the residual volume. At the last examina-

Longitudinal study of lung volumes in asthmatic children (VII)

tion—after about four years—the lung volumes of the asthmatic children differed only slightly from those of healthy children. The successively reduced hyperinflation accordingly showed that the cause of the marked hyperinflation at the first examination of these symptom-free asthmatic children was reversible and therefore could be considered to be of a functional nature. Since the children in the longitudinal study were selected from among those included in the cross-sectional study of lung volumes in symptom-free asthmatic children (II), it may be assumed that the results are representative of asthmatic patients with disturbed lung function treated at this Department for Allergic Children.

*Significance for
clinical assess-
ment*

Comparison of the clinical classifications of severity of asthma with the results of the different cross-sectional studies of lung function in symptom-free asthmatic children shows close agreement when the material is considered as a group. The progressive normalization of lung volumes during the four years in which the children were under observation also correlates well with the clinical assessments of their course, both on the basis of attack rate alone and of the course as a whole. But in individual cases there have been discrepancies between the clinical assessment and the results of lung function tests. Many patients clinically classified as comparatively mild cases have more or less pronounced changes in lung function while in the different groups, especially in Groups I and II, there are cases who do not deviate from the normal. The combined use of clinical data and results of lung function tests increase the reliability of assessment of the severity of individual cases. The finding of hyperinflation in one lung function test may, however, be ascribable to a recent attack which has not yet completely disappeared, and repeated examinations will therefore give a more representative indication of the individual's condition.

It has been found that these examinations of lung function, which have been conducted in direct association with the clinical care of the asthmatic children, can, without difficulty, be linked to the routine care and follow-up procedure. Cooperation from the child, however, is essential, and for successful results the staff must not only be familiar with the apparatus and method, but must have a considerable experience of handling children. The apparatus must be adopted for use in children. Although duplicate tests of lung volumes and testing of timed vital capacity take about 90 minutes (including rest periods), the children have shown no signs of discomfort. The need for active cooperation of the child and for breathing through a mouthpiece places the lower age limit for these tests at about 6 years.

The fact that a large group of asthmatic children manifests disturbance of lung function even during symptom-free periods must affect the attitude concerning the therapy. Hyperinflation and diminished capacity of forced ex-

piration are at least partially due to bronchial obstruction, and it should be of importance that children with signs of disturbed lung function receive prolonged treatment with bronchodilator drugs, even during symptom-free periods, in addition to general anti-allergic treatment. Since there is not always close correlation between clinical evaluation and findings from lung function tests, a careful follow-up of the lung function in asthmatic children will be of good help for regulating the intensity and duration of therapy. The introduction of continuous lung function tests in the care of asthmatic children also provides increased possibilities of judging the effect of different forms of therapy.

Summary

Lung function tests (lung volumes, maximal breathing capacity and timed vital capacity) performed in asthmatic children during symptom-free intervals show that the lung function of asthmatic children, considered as a group, differs from that in healthy children in form of hyperinflation of the lungs and diminished capacity of forced expiration.

The determination of lung volumes before and after administration of bronchodilator drugs in cases with marked hyperinflation of the lungs in clinically symptom-free periods shows at least a partly functional origin of the changes. A follow-up study of the lung volumes of a group of children undergoing long-term treatment with initial hyperinflation of the lungs shows the reversibility of the changes.

The clinical evaluation of the severity of the asthma correlates well with the results of lung function tests when the material is considered as a group, but in individual cases there are often discrepancies. The study of lung function will broaden the evaluation of asthma in individual cases and increase the reliability of assessing the therapy and prognosis. Lung function tests also provide increased possibilities of objectively recording the effect of various therapies.

The lung function tests employed, especially the determination of lung volumes and timed vital capacity, are easy to perform, even in children, and can form part of the routine care and follow-up of asthmatic children.

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